DISSOCIATION CONSTANTS OF SOME COMPOUNDS RELATED TO LYSERGIC ACID

PART II. ERGOMETRINE, ERGOMETRININE AND ALKANOLAMIDES OF 3-DIMETHYLAMINOPROPIONIC ACID, 1-METHYLHEXAHYDRONICOTINIC ACID AND ARECAIDINE

BY J. CHILTON AND J. B. STENLAKE

From the Department of Pharmacy, The Royal College of Science and Technology, Glasgow

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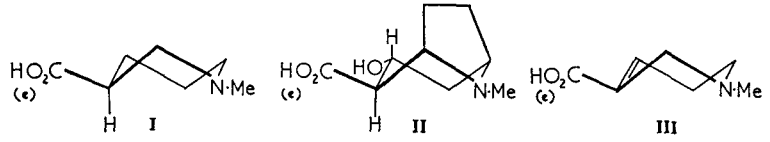
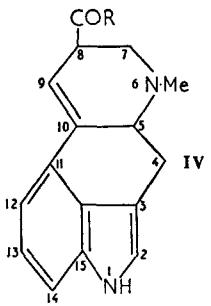
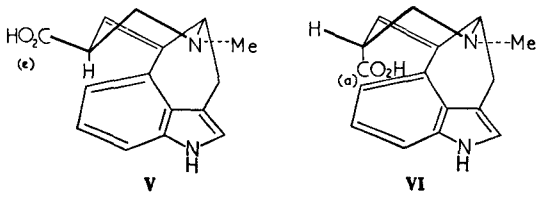
Dissociation constants have been recorded for ergometrine, ergometrinine and a number of alkanolamides of 3-dimethylaminopropionic acid, 1-methylhexahydronicotinic acid and arecaidine. The similarity of ΔpK (amide) values for the alkanolamides with that for ergometrine, offers evidence that such values may be taken as an indicator of amino-carboxyl distances.

IN a previous communication (Chilton and Stenlake, 1955) ΔpK (ester) values (the difference between the $pK'a_2$ value of an amino-acid and the pK'a value of its ester) for 3-dimethylaminopropionic acid, 1-methylhexahydronicotinic acid, ψ-ecgonine and arecaidine were shown to be similar, indicating that there is a similar relationship of amino- and carboxyl groups in all of these compounds (Neuberger, 1937) consistent with the adoption of a chair ring-conformation and an equatorial carboxyl substituent by the last three (structures I, II, and III respectively).







A similar comparison of ΔpK (ester) values for lysergic and isolysergic acids (IV; R=OH) in aqueous solution was prevented by the low water-solubility of their esters. The higher water-solubility of ergometrine and ergometrinine (IV; R=NHCH(Me)CH_2OH), however, allowed determination of differences in pK'a between these alkanolamides and the corresponding acids (ΔpK (amide) values). Agreement between ΔpK (amide) values for ergometrine with those for the alkanolamides of 3-dimethylaminopropionic acid, 1-methylhexahydronicotinic acid and arecaidine (Table I) offers evidence that this value, like the ΔpK (ester) value, is a measure of amino-carboxyl distance in related molecules and that there is a similar steric relationship of amino- and carboxyl groups in all of these compounds. This would be in agreement with the previously postulated (Stenlake, 1953) adoption of a semi-chair conformation by ring D of lysergic acid and ergometrine in aqueous solution, combined with a equatorial substituent at C(8) (structure V corresponding to structures I and II for the other cyclic amino-acids).

TABLE I

DIFFERENCES IN pK'A VALUES BETWEEN AMINO-ACIDS AND THEIR ALKANOLAMIDES (Δ pK (AMIDE) VALUES)

Amino-acid	pK'a values of			ΔpK (amide)
	Acid	Ethanolamide	Propanolamide	
3-Dimethylaminopropionic acid	9·85	8·65	8·82	1·20 1·03
1-Methylhexahydronicotinic acid	9·70	8·65		1·05
1-Methyl- 1,2,5,6- tetrahydronicotinic acid ..	9·07	8·02	8·07	1·05 1·00
Lysergic acid (in 40 per cent cellosolve, 7·84; in 30 per cent cellosolve, 7·82; in 15 per cent cellosolve, 7·84)	7·83		6·79	1·04
Isolysergic acid (in 30 per cent cellosolve, 8·69; in 20 per cent cellosolve, 8·68)	8·68		7·37	1·31

The higher ΔpK (amide) value for ergometrinine (Table I) supports the validity of our interpretation of ΔpK (amide) values and the existence of an axial carboxyl substituent at C(8) in the isolysergic acid series (VI); it is analogous to the higher ΔpK (ester) value of ecgonine, which is known to have an axial carboxyl substituent as compared with ψ-ecgonine and other related molecules with equatorial carboxyl groups (Chilton and Stenlake, 1955). It would be expected that the closer proximity of ionised carboxyl and amino-groups produced by an axial configuration of the carboxyl group would have a base-strengthening effect in the free acid (Stenlake, 1953) whereas the effect of a proximate carboxypropanolamido-group on the ionisation of the basic nitrogen would only be the relatively weak one due to hydrogen bonding with the amido and hydroxyl hydrogen atoms. This hydrogen bonding would have the effect of increasing the pK'a value of the alkanolamide relative to that of the corresponding ester in which bonding could not occur, and would result in a ΔpK (amide) value lower than that of the ΔpK (ester) value for the same amino-acid. This is shown clearly in values quoted by Stoll and co-workers (1954) for the dihydroisolysergic acid series: for dihydroisolysergic

acid I and its monoethyl amide ΔpK (amide) = 1·97 while ΔpK (ester) = 2·85. The effect is much less marked in the corresponding dihydrolysergic acid derivatives, where an equatorial carboxyl substituent would result in wider separation of the interacting groups (dihydrolysergic acid I has ΔpK (amide) 1·17 and ΔpK (ester) 1·65). The difference in actual values between these figures and our own may be attributed to the use of 80 per cent cellosolve as solvent by Stoll. It follows that the ΔpK (amide) value would not be expected to vary so much with differences in distance between amino- and carboxyl groups as does the ΔpK (ester) value. The relatively small, though significant, differences between ΔpK (amide) values for lysergic and isolysergic acids would therefore probably have corresponded to a much greater difference in ΔpK (ester) values if these had been obtainable in an aqueous system and both methods should be equally valid as a means of comparing differences in distance between charged groups in related molecules.

Experimental

Dissociation constants were determined by titration of the hydrochlorides of the bases in aqueous solution (0·005 M) at 25° with carbonate-free potassium hydroxide solution as described by Chilton and Stenlake (1955). Lysergic and isolysergic acids, which are not soluble in water to this extent at 25°, were dissolved in a known slight excess of carbonate-free potassium hydroxide solution and immediately back-titrated with 0·05 N hydrochloric acid. The addition of a little ethyl cellosolve was found necessary to prevent precipitation during titration, but was considered to have little effect on ionisation, since pK'a values determined at a number of different low cellosolve concentrations showed no marked or consistent variation (Table I).

Preparation of Materials

2-(3'-Dimethylaminopropionamido)ethanol, (±)-2-(3'-dimethylaminopropionamido)propanol and 2-(1'-methylhexahydronicotinamido)ethanol hydrochlorides. The acid oxalates, prepared by the method of Chilton and Stenlake (1962), were converted to hydrochlorides as follows: 0·1 millimole of the oxalate dissolved in water (1 ml.) was treated with a very small excess of solution of calcium chloride (10 per cent). Precipitated calcium oxalate was removed by centrifugation, washed with water and the total aqueous solutions made up accurately to 5 ml. with water. Aliquot portions of 1 ml. (0·02 millimole) were used for titration.

2-(1'-Methyl-1',2',5',6'-tetrahydronicotinamido)ethanol and (±)-2-(1'-methyl-1',2',5',6'-tetrahydronicotinamido)propanol hydrochlorides. Prepared by treatment of aqueous solutions of the dihydrochlorides of 2-aminoethyl 1,2,5,6-tetrahydronicotinate and (±)-2-aminopropyl 1,2,5,6-tetrahydronicotinate respectively with a slight excess of sodium hydroxide followed by neutralisation with dilute hydrochloric acid as described by Chilton and Stenlake (1962). The neutralised solution was used directly for titration.

Ergometrine and ergometrinine hydrochlorides. Authentic samples of the bases, kindly given by Messrs. Burroughs Wellcome & Co. Ltd., were dissolved in a known slight excess of hydrochloric acid immediately before titration.

Lysergic acid was prepared from ergotoxine by the method of Stoll and Hofmann (1937), m.p. 239° (decomp.) from water. Stoll and Hofmann (1937) give 240–250° (decomp.).

Isolysergic acid was prepared from lysergic acid by the method of Smith and Timmis (1936), m.p. 238° (decomp.) from water, depressed on mixture with lysergic acid. Stoll and Hofmann (1937) give 240–245°. The equivalent weight and homogeneity of this acid and of the lysergic acid were confirmed from their neutralisation curves.

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